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Development

Indian hedgehog activates hematopoiesis and vasculogenesis and can respecify prospective neurectodermal cell fate in the mouse embryo.

Dyer MA, Farrington SM, Mohn D, Munday JR, Baron MH.

Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA. margaret.baron@mssm.edu

During gastrulation in the mouse, mesoderm is induced and patterned by secreted signaling molecules, giving rise first to primitive erythroblasts and vascular endothelial cells. We have demonstrated previously that development of these lineages requires a signal(s) secreted from the adjacent primitive endoderm. We now show that Indian hedgehog (Ihh) is a primitive endoderm-secreted signal that alone is sufficient to induce formation of hematopoietic and endothelial cells. Strikingly, as seen with primitive endoderm, Ihh can respecify prospective neural ectoderm (anterior epiblast) along hematopoietic and endothelial (posterior) lineages. Downstream targets of the hedgehog signaling pathway (the genes encoding patched, smoothened and Gli1) are upregulated in anterior epiblasts cultured in the presence of Ihh protein, as is Bmp4, which may mediate the effects of Ihh. Blocking Ihh function in primitive endoderm inhibits activation of hematopoiesis and vasculogenesis in the adjacent epiblast, suggesting that Ihh is an endogenous signal that plays a key role in the development of the earliest hemato-vascular system. To our knowledge, these are the earliest functions for a hedgehog protein in post-implantation development in the mouse embryo.

PMID: 11311154 [PubMed - in process]

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EXHIBIT B

1: Nat Immunol 2001 Feb;2(2):172-80

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nature immunology

Sonic hedgehog induces the proliferation of primitive human hematopoietic cells via BMP regulation.

Bhardwaj G, Murdoch B, Wu D, Baker DP, Williams KP, Chadwick K, Ling LE, Karanu FN, Bhatia M.

John P. Robarts Research Institute, Developmental Stem Cell Biology, 100 Perth Drive, London, Ontario N6A 5K8, Canada.

A pool of stem cells that arise from the mesoderm during embryogenesis initiates hematopoiesis. However, factors that regulate the expansion of blood stem cells are poorly understood. We show here that cytokine-induced proliferation of primitive human hematopoietic cells could be inhibited with antibodies to hedgehog (Hh). Conversely, Sonic hedgehog (Shh) treatment induced the expansion of pluripotent human hematopoietic repopulating cells detected in immunodeficient mice. Noggin, a specific inhibitor of bone morphogenetic protein 4 (BMP-4), was capable of inhibiting Shh-induced proliferation in a similar manner to anti-Hh; however, anti-Hh had no effect on BMP-4-induced proliferation. Our study shows that Shh functions as a regulator of primitive hematopoietic cells via mechanisms that are dependent on downstream BMP signals.

PMID: 11175816 [PubMed - indexed for MEDLINE]

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